

# Chemical Abstracts

09/926,693

*cf Florence  
since 2/19/03*

June 11, 2002

=> d que 17

L1	1	SEA	FILE=REGISTRY	ABB=ON	PLU=ON	RILUZOLE/CN
L2	5529	SEA	FILE=HCAPLUS	ABB=ON	PLU=ON	"MULTIPLE SCLEROSIS"/CT
L3	260	SEA	FILE=HCAPLUS	ABB=ON	PLU=ON	L1
L4	3	SEA	FILE=HCAPLUS	ABB=ON	PLU=ON	L2 AND L3
L5	157	SEA	FILE=HCAPLUS	ABB=ON	PLU=ON	L1(L)THU/RL
L6	3	SEA	FILE=HCAPLUS	ABB=ON	PLU=ON	L2 AND L5
L7	3	SEA	FILE=HCAPLUS	ABB=ON	PLU=ON	L4 OR L6

L7 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2002 ACS  
AN 2001:923612 HCAPLUS  
DN 136:42875  
TI Pharmaceutical composition containing Riluzole for the treatment of  
multiple sclerosis  
IN Melamed, Eldad; Ophen, Daniel  
PA Mor - Research Applications Ltd., Israel  
SO PCT Int. Appl., 17 pp.  
CODEN: PIXXD2  
DT Patent  
LA English  
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001095907	A1	20011220	WO 2001-IL534	20010612
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRAI IL 2000-136687 A 20000612

AB An oral pharmaceutical compn. for the treatment of multiple sclerosis (MS) comprises a pharmaceutically acceptable carrier and as an active ingredient, Riluzole. Riluzole, a drug that inhibits glutamatergic release, is shown to be effective in the prevention and treatment of MS. The effect of Riluzole is shown in an animal model of MS, an exptl. autoimmune encephalomyelitis (EAE) model produced by injection of myelin oligodendrocyte glycoprotein (MOG) to animals. Administration of Riluzole to such animals before they develop the MS-related symptoms markedly reduced the incidence and clin. severity of the disease in such animals. Moreover, treatment of such animals after the appearance of severe MS-related symptoms, also markedly slowed down the progression of the disease and improved the clin. manifestations.

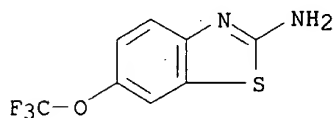
IT 1744-22-5, Riluzole

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(oral compn. contg. Riluzole for treatment of multiple sclerosis)

RN 1744-22-5 HCAPLUS

CN 2-Benzothiazolamine, 6-(trifluoromethoxy)- (9CI) (CA INDEX NAME)



IC ICM A61K031-428

ICS A61P025-00

CC 63-6 (Pharmaceuticals)

Section cross-reference(s): 1

ST Riluzole oral multiple sclerosis  
 IT Glycoproteins  
 RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)  
 (MOG (myelin-oligodendroglial glycoprotein); oral compn. contg.  
 Riluzole for treatment of multiple sclerosis in MOG-induced autoimmune  
 encephalomyelitis as animal model)  
 IT Encephalomyelitis  
 (autoimmune; oral compn. contg. Riluzole for treatment of multiple  
 sclerosis in autoimmune encephalomyelitis as animal model)  
 IT Disease models  
 (oral compn. contg. Riluzole for treatment of multiple sclerosis in  
 autoimmune encephalomyelitis as animal model)  
 IT Drug delivery systems  
 (oral; oral compn. contg. Riluzole for treatment of multiple sclerosis)  
 IT **Multiple sclerosis**  
 (therapeutic agents; oral compn. contg. Riluzole for treatment of  
 multiple sclerosis)  
 IT **1744-22-5, Riluzole**  
 RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL  
 (Biological study); USES (Uses)  
 (oral compn. contg. Riluzole for treatment of multiple sclerosis)  
 RE.CNT 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD  
 ALL CITATIONS AVAILABLE IN THE RE FORMAT

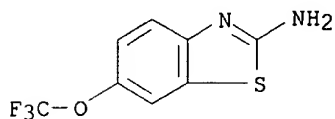
L7 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2002 ACS  
 AN 2000:880959 HCAPLUS  
 DN 134:25377  
 TI Use of riluzole for the treatment of multiple sclerosis  
 IN Polman, Chris  
 PA Vereniging Voor Christelijk Wetenschappelijk Onderwijs, Neth.; Biogen,  
 Inc.  
 SO PCT Int. Appl., 15 pp.  
 CODEN: PIXXD2  
 DT Patent  
 LA English  
 FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2000074676	A1	20001214	WO 2000-IB933	20000602
	W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
	EP 1187612	A1	20020320	EP 2000-939007	20000602
	R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO			
PRAI	EP 1999-201788	A	19990604		
	US 2000-174328P	P	20000104		
	WO 2000-IB933	W	20000602		
AB	Methods and compns. are provided for the treatment of multiple sclerosis with riluzole [6-(trifluoromethoxy)-benzothiazolamine].				
IT	1744-22-5, Riluzole				

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(riluzole for multiple sclerosis treatment)

RN 1744-22-5 HCAPLUS

CN 2-Benzothiazolamine, 6-(trifluoromethoxy)- (9CI) (CA INDEX NAME)



IC ICM A61K031-425

CC 1-11 (Pharmacology)

Section cross-reference(s): 63

ST riluzole multiple sclerosis

IT Drug delivery systems

(riluzole for multiple sclerosis treatment)

IT **Multiple sclerosis**

(therapeutic agents; riluzole for multiple sclerosis treatment)

IT Interferons

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(.beta.1, .beta.1a and .beta.1b; riluzole for multiple sclerosis treatment)

IT 1744-22-5, Riluzole 147245-92-9, Copaxone

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(riluzole for multiple sclerosis treatment)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD  
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2002 ACS

AN 1998:640417 HCAPLUS

DN 129:239904

TI Method of evaluating the efficacy of drug on brain nerve cells using measurement of N-acetylaspartate with magnetic resonance spectroscopy

IN Arnold, Douglas L.; Cashman, Neil; Kalra, Sanjay

PA Can.

SO PCT Int. Appl., 22 pp.

CODEN: PIXXD2

DT Patent

LA English

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9841882	A1	19980924	WO 1998-CA230	19980313

W: CA, US

RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRAI CA 1997-2200045 19970314

AB A method is provided for measurement in vivo of the effect of a drug on the function of the nerve cells of the brain of a patient suffering from a

neurol. disease. The method comprises (a) measuring N-acetylaspartate (NAA) signal intensity using magnetic resonance spectroscopy (MRS) of the brain of the patient; (b) subjecting the patient to a treatment with the drug to be tested and measuring NAA signal intensity using MRS of the brain of the patient; and (c) comparing the spectra of steps (a) and (b) to det. whether the drug has an effect on the function of the nerve cells of the brain. An increase in the NAA signal of step (b) is indicative of a drug with a pos. effect.

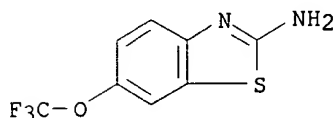
IT 1744-22-5, Riluzole

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(evaluation of efficacy of drugs on brain nerve cells using measurement of acetylaspartate with magnetic resonance spectroscopy)

RN 1744-22-5 HCAPLUS

CN 2-Benzothiazolamine, 6-(trifluoromethoxy)- (9CI) (CA INDEX NAME)



IC ICM G01R033-483

CC 1-11 (Pharmacology)

Section cross-reference(s): 8

ST drug effect brain disorder acetylaspartate MRS; magnetic resonance spectroscopy acetylaspartate brain disorder; neuron brain magnetic resonance spectroscopy acetylaspartate

IT Imaging

(NMR; evaluation of efficacy of drugs on brain nerve cells using measurement of acetylaspartate with magnetic resonance spectroscopy)

IT Nervous system

(amyotrophic lateral sclerosis; evaluation of efficacy of drugs on brain nerve cells using measurement of acetylaspartate with magnetic resonance spectroscopy)

IT Nervous system

(degeneration; evaluation of efficacy of drugs on brain nerve cells using measurement of acetylaspartate with magnetic resonance spectroscopy)

IT Nervous system

(disease; evaluation of efficacy of drugs on brain nerve cells using measurement of acetylaspartate with magnetic resonance spectroscopy)

IT Anti-Alzheimer's agents

Anticonvulsants

Brain

**Multiple sclerosis**

Nervous system agents

(evaluation of efficacy of drugs on brain nerve cells using measurement of acetylaspartate with magnetic resonance spectroscopy)

IT Spectroscopy

(magnetic resonance; evaluation of efficacy of drugs on brain nerve cells using measurement of acetylaspartate with magnetic resonance spectroscopy)

IT Nerve

(neuron; evaluation of efficacy of drugs on brain nerve cells using measurement of acetylaspartate with magnetic resonance spectroscopy)

IT Brain, disease  
(stroke; evaluation of efficacy of drugs on brain nerve cells using measurement of acetylaspartate with magnetic resonance spectroscopy)

IT 1744-22-5, Riluzole 2156-56-1, Sodium dichloroacetate  
30516-87-1, Zidovudine 60142-96-3, Gabapentin  
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)  
(evaluation of efficacy of drugs on brain nerve cells using measurement of acetylaspartate with magnetic resonance spectroscopy)

IT 57-00-1, Creatine 997-55-7  
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)  
(evaluation of efficacy of drugs on brain nerve cells using measurement of acetylaspartate with magnetic resonance spectroscopy)

# MEDLINE

09/926,693

June 11, 2002

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L9	275	SEA	FILE=MEDLINE	ABB=ON	PLU=ON	RILUZOLE/CT
L10	20258	SEA	FILE=MEDLINE	ABB=ON	PLU=ON	MULTIPLE SCLEROSIS+NT/CT
L11	1	SEA	FILE=MEDLINE	ABB=ON	PLU=ON	L9 AND L10

L11 ANSWER 1 OF 1 MEDLINE  
 ACCESSION NUMBER: 1999424113 MEDLINE  
 DOCUMENT NUMBER: 99424113 PubMed ID: 10494326  
 TITLE: [New therapies in neurology, but who benefits?].  
 Nieuwe therapieën in de neurologie, maar wie wordt er beter van?.  
 AUTHOR: Vermeulen M; de Haan R J  
 CORPORATE SOURCE: Afd. Neurologie, Academisch Medisch Centrum, Amsterdam.  
 SOURCE: NEDERLANDS TIJDSCHRIFT VOOR GENEESKUNDE, (1999 Aug 28) 143  
 (35) 1764-6. Ref: 11  
 Journal code: 0400770. ISSN: 0028-2162.  
 PUB. COUNTRY: Netherlands  
 Journal; Article; (JOURNAL ARTICLE)  
 General Review; (REVIEW)  
 (REVIEW, TUTORIAL)  
 LANGUAGE: Dutch  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199910  
 ENTRY DATE: Entered STN: 20000111  
 Last Updated on STN: 20000111  
 Entered Medline: 19991029  
 AB In recent years several new treatments have been introduced in neurology, sumatriptan in migraine, riluzole in amyotrophic lateral sclerosis, interferon-beta in multiple sclerosis and rivastigmine in Alzheimer's disease. Doubts exist on the effects on functional outcome of these new treatments. Hardly effective drugs are not forced on physicians by the pharmaceutical industry, since physicians are involved in decisions from phase I studies to the final approval of the drugs. The problem is, however, that in clinical studies emphasis is still on statistically significant differences rather than on meaningful differences in the functional status of patients. In conclusion, in clinical studies outcome measures should be chosen more carefully and there is a need for sensitive linear functional scales.  
 CT Check Tags: Human  
 Alzheimer Disease: DT, drug therapy  
 Amyotrophic Lateral Sclerosis: DT, drug therapy  
 Antiviral Agents: TU, therapeutic use  
 Carbamates: TU, therapeutic use  
 English Abstract  
 Interferon-beta: TU, therapeutic use  
 Migraine: DT, drug therapy  
**Multiple Sclerosis: DT, drug therapy**  
 \*Nervous System Diseases: DT, drug therapy  
 Netherlands  
 Neuroprotective Agents: TU, therapeutic use  
 \*Outcome Assessment (Health Care): MT, methods  
**Riluzole: TU, therapeutic use**  
 Sumatriptan: TU, therapeutic use  
 Vasoconstrictor Agents: TU, therapeutic use  
 RN 103628-46-2 (Sumatriptan); 123441-03-2 (rivastigmine); 1744-22-5 (Riluzole); 77238-31-4 (Interferon-beta)  
 CN 0 (Antiviral Agents); 0 (Carbamates); 0 (Neuroprotective Agents); 0 (Vasoconstrictor Agents)



09/926,693

June 11, 2002

=> d que

L9	275	SEA	FILE=MEDLINE	ABB=ON	PLU=ON	RILUZOLE/CT
L14	71529	SEA	FILE=MEDLINE	ABB=ON	PLU=ON	SPINAL CORD?/CT
L15	18	SEA	FILE=MEDLINE	ABB=ON	PLU=ON	L9 AND L14

L15 ANSWER 1 OF 18 MEDLINE  
 ACCESSION NUMBER: 2001229774 MEDLINE  
 DOCUMENT NUMBER: 21196980 PubMed ID: 11302627  
 TITLE: Evaluation of the neuroprotective effects of sodium channel blockers after spinal cord injury: improved behavioral and neuroanatomical recovery with riluzole.  
 AUTHOR: Schwartz G; Fehlings M G  
 CORPORATE SOURCE: Division of Cell and Molecular Biology, The Toronto Western Research Institute, Ontario, Canada.  
 SOURCE: JOURNAL OF NEUROSURGERY, (2001 Apr) 94 (2 Suppl) 245-56. Journal code: 0253357. ISSN: 0022-3085.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
 ENTRY MONTH: 200104  
 ENTRY DATE: Entered STN: 20010502  
 Last Updated on STN: 20010502  
 Entered Medline: 20010426

AB OBJECT: Persistent activation of voltage-sensitive Na<sup>+</sup> channels is associated with cellular toxicity and may contribute to the degeneration of neural tissue following traumatic brain and spinal cord injury (SCI). Pharmacological blockade of these channels can attenuate secondary pathophysiology and reduce functional deficits acutely. METHODS: To determine the therapeutic effects of Na<sup>+</sup> channel blockers on long-term tissue sparing and functional neurological recovery after traumatic SCI, the authors injected Wistar rats intraperitoneally with riluzole (5 mg/kg), phenytoin (30 mg/kg), CNS5546A, a novel Na<sup>+</sup> channel blocker (15 mg/kg), or vehicle (2-HP3CD; 5 mg/kg) 15 minutes after induction of compressive SCI at C7-T1. Functional neurological recovery of coordinated hindlimb function and strength, assessed 1 week postinjury and weekly thereafter for 6 weeks, was significantly enhanced in animals treated with riluzole compared with the other treatment groups. Seven weeks postinjury the preservation of residual tissue and integrity of descending axons were determined with digital morphometrical and fluorescent histochemical analysis. All three Na<sup>+</sup> channel blockers significantly enhanced residual tissue area at the injury epicenter compared with control. Riluzole significantly reduced tissue loss in rostrocaudal regions surrounding the epicenter, with overall sparing of gray matter and selective sparing of white matter. Also, counts of red nuclei neurons retrogradely labeled with fluorogold introduced caudal to the injury site were significantly increased in the riluzole group. CONCLUSIONS: Systemic Na<sup>+</sup> channel blockers, in particular riluzole, can confer significant neuroprotection after in vivo SCI and result in behavioral recovery and sparing of both gray and white matter.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't  
 Axons: DE, drug effects  
 Axons: PA, pathology  
 Behavior, Animal: DE, drug effects  
 Efferent Pathways: DE, drug effects  
 Efferent Pathways: PA, pathology  
 \*Neuroprotective Agents: TU, therapeutic use  
 Rats  
 Rats, Wistar  
 \*Riluzole: TU, therapeutic use  
 \*Sodium Channel Blockers

Spinal Cord: DE, drug effects  
 Spinal Cord: PA, pathology  
 Spinal Cord: PP, physiopathology  
 Spinal Cord Compression: ET, etiology  
 Spinal Cord Injuries: CO, complications  
 \*Spinal Cord Injuries: DT, drug therapy  
 Spinal Cord Injuries: PA, pathology  
 Spinal Cord Injuries: PX, psychology

RN 1744-22-5 (Riluzole)

CN 0 (Neuroprotective Agents); 0 (Sodium Channel Blockers)

L15 ANSWER 2 OF 18

MEDLINE

ACCESSION NUMBER: 2001132615 MEDLINE

DOCUMENT NUMBER: 20575755 PubMed ID: 11135009

TITLE: The effect of riluzole treatment in rats on the survival of injured adult and grafted embryonic motoneurons.

AUTHOR: Nogradi A; Vrbova G

CORPORATE SOURCE: Department of Ophthalmology, Albert Szent-Gyorgyi Medical Centre, University of Szeged, 6720-SzegedKoranyi fasor 10-11, Hungary.. nogradi@poht.szote.u-szeged.hu

SOURCE: EUROPEAN JOURNAL OF NEUROSCIENCE, (2001 Jan) 13 (1) 113-8. Journal code: 8918110. ISSN: 0953-816X.

PUB. COUNTRY: France  
 Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200103

ENTRY DATE: Entered STN: 20010404  
 Last Updated on STN: 20010404  
 Entered Medline: 20010301

AB The effect of riluzole on the survival of injured motoneurons was studied. The L4 ventral root was avulsed and reimplanted into the spinal cord. Immediately after the operation, 4 animals were treated with riluzole for 3 weeks while another 4 animals received no treatment after the operation. Three months later the fluorescent dyes, Fast Blue and Diamidino Yellow, were applied to the cut ventral ramus of the L4 spinal nerve, for retrograde labelling of neurons. Three days later, the spinal cords were processed to reveal the retrograde-labelled cells. In untreated animals, there were 20 +/- 2.1 labelled neurons (+/- SEM), while in animals treated with riluzole there were 723 +/- 26. Thus, treatment with riluzole dramatically enhanced the survival of injured motoneurons. In another series of experiments, after avulsion of the L4 ventral root and its reinsertion, embryonic spinal cord pieces were grafted into the host cord. Five animals received riluzole treatment and 4 were left untreated. In the untreated animals, 125 +/- 5.1 retrograde-labelled cells of both graft and host origin were detected. In rats treated with riluzole, 645 +/- 35.7 retrograde-labelled cells were seen and almost all of these were of host origin. Thus, treatment with riluzole enhanced the survival of injured host motoneurons, and by doing so, (i) reduced the ability of grafted neurons to extend their axons into the reimplanted L4 ventral root, and (ii) reduced the survival of the grafted cells.

CT Check Tags: Animal; Support, Non-U.S. Gov't

Cell Survival: DE, drug effects

Embryo

Motor Neurons: DE, drug effects

\*Motor Neurons: PH, physiology

\*Motor Neurons: TR, transplantation

Nerve Regeneration  
 \*Neuroprotective Agents: PD, pharmacology  
 Rats  
 Rats, Wistar  
 \*Replantation  
 \*Riluzole: PD, pharmacology  
 \*Spinal Cord: SU, surgery  
 \*Spinal Nerve Roots: IN, injuries  
 Spinal Nerve Roots: PA, pathology  
 \*Spinal Nerve Roots: PP, physiopathology

RN 1744-22-5 (Riluzole)  
 CN 0 (Neuroprotective Agents)

L15 ANSWER 3 OF 18 MEDLINE  
 ACCESSION NUMBER: 2001029518 MEDLINE  
 DOCUMENT NUMBER: 20500776 PubMed ID: 11046220  
 TITLE: Neuroprotective effects of riluzole and ketamine during transient spinal cord ischemia in the rabbit.  
 AUTHOR: Lips J; de Haan P; Bodewits P; Vanicky I; Dzoljic M; Jacobs M J; Kalkman C J  
 CORPORATE SOURCE: Academic Medical Center, University of Amsterdam, The Netherlands.  
 SOURCE: ANESTHESIOLOGY, (2000 Nov) 93 (5) 1303-11.  
 Journal code: 1300217. ISSN: 0003-3022.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
 ENTRY MONTH: 200011  
 ENTRY DATE: Entered STN: 20010322  
 Last Updated on STN: 20010322  
 Entered Medline: 20001121

AB BACKGROUND: Massive release of central excitatory neurotransmitters is an important initial step in ischemic neuronal injury, and modification of this process may provide neuroprotection. We studied the protective effects of the voltage-dependent sodium channel antagonist riluzole and the N-methyl-D-aspartate receptor antagonist ketamine on hind limb motor function and histopathologic outcome in an experimental model of spinal cord ischemia. METHODS: Temporary spinal cord ischemia was induced by 29 min of infrarenal balloon occlusion of the aorta in 60 anesthetized New Zealand white rabbits. Animals were randomly assigned to one of four treatment groups (n = 15 each): group C, saline (control); group R, riluzole, 8 mg/kg intravenously; group K, ketamine, 55 mg/kg intravenously; group RK, riluzole and ketamine. After reperfusion, riluzole treatment was continued with intraperitoneal infusions. Normothermia (38 degrees C) was maintained during ischemia, and rectal temperature was assessed before and after intraperitoneal infusions. Neurologic function, according to Tarlov's criteria, was evaluated every 24 h, and infarction volume and the number of eosinophilic neurons and viable motoneurons in the lumbosacral spinal cord was evaluated after 72 h. RESULTS: Neurologic outcome was better in groups R and RK than in groups C and K. All animals in group C (100%) and all animals but one in group K (93%) were paraplegic 72 h after the ischemic insult versus 53% in group R and 67% in group RK (P < 0.01 each). More viable motoneurons were present in groups R and RK than in controls (P < 0.05). CONCLUSIONS: The data indicate that treatment with riluzole can increase the tolerance of spinal cord motoneurons to a period of normothermic ischemia.

Intraischemic ketamine did not provide neuroprotection in this model.

CT Check Tags: Animal; Comparative Study; Support, Non-U.S. Gov't  
 Disease Models, Animal  
 Excitatory Amino Acid Antagonists: PD, pharmacology  
 Infarction: ET, etiology  
 Infarction: PA, pathology  
 Infarction: PC, prevention & control  
 \*Ketamine: PD, pharmacology  
 \*Neuroprotective Agents: PD, pharmacology  
 Paraplegia: ET, etiology  
 Paraplegia: PC, prevention & control  
 Rabbits  
 \*Riluzole: PD, pharmacology  
 Spinal Cord: BS, blood supply  
 Spinal Cord: PA, pathology  
 Spinal Cord Ischemia: CO, complications  
 \*Spinal Cord Ischemia: DT, drug therapy

RN 1744-22-5 (Riluzole); 6740-88-1 (Ketamine)  
 CN 0 (Excitatory Amino Acid Antagonists); 0 (Neuroprotective Agents)

L15 ANSWER 4 OF 18 MEDLINE  
 ACCESSION NUMBER: 2000470324 MEDLINE  
 DOCUMENT NUMBER: 20359137 PubMed ID: 10899284  
 TITLE: Riluzole increases high-affinity glutamate uptake in rat spinal cord synaptosomes.  
 AUTHOR: Azbill R D; Mu X; Springer J E  
 CORPORATE SOURCE: Department of Anatomy and Neurobiology, Spinal Cord and Brain Injury Research Center, University of Kentucky Medical Center, Lexington, KY 40536-0084, USA.  
 CONTRACT NUMBER: NS-30248 (NINDS)  
 SOURCE: BRAIN RESEARCH, (2000 Jul 21) 871 (2) 175-80.  
 Journal code: 0045503. ISSN: 0006-8993.  
 PUB. COUNTRY: Netherlands  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200010  
 ENTRY DATE: Entered STN: 20001012  
 Last Updated on STN: 20001012  
 Entered Medline: 20001004

AB The purpose of this study was to examine the effect of the anti-convulsant agent, riluzole, on high-affinity glutamate uptake as measured in rat spinal cord synaptosomes. The rate of glutamate uptake was significantly increased in the presence of 0.1 microM and 1.0 microM riluzole, but not at the higher concentrations examined. Kinetics analysis demonstrated that riluzole (0.1 microM) decreased the apparent K(m) by 21% and increased the V(max) by 31%. Glutamate uptake also was significantly increased in spinal cord synaptosomes obtained from rats treated with 8 mg/kg (i.p.) of riluzole and sacrificed 4 h later. The increase in glutamate uptake in vitro was not affected by pretreatment either with H7, an inhibitor of PKA and PKC, or with the PKC activating phorbol ester, 12-O-tetradecanoylphorbol 13-acetate. Previous studies have shown that some of the actions of riluzole are mediated by G proteins sensitive to pertussis toxin. Surprisingly, treatment of synaptosomes with pertussis toxin alone increased the rate of glutamate uptake, while having no effect on uptake in the presence of riluzole. However, pretreatment with cholera toxin was found to completely block the effects of riluzole on glutamate uptake.

These results reveal an additional mechanism by which riluzole can affect glutamatergic neurotransmission, and provides further support that riluzole may prove beneficial in the treatment of traumatic central nervous system injuries involving the excitotoxic actions of glutamate.

CT Check Tags: Animal; Female; Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

\*ATP-Binding Cassette Transporters: DE, drug effects

\*ATP-Binding Cassette Transporters: ME, metabolism

Amino Acid Transport System X-AG

Dose-Response Relationship, Drug

GTP-Binding Proteins: DE, drug effects

GTP-Binding Proteins: ME, metabolism

\*Glutamic Acid: ME, metabolism

Rats

Rats, Long-Evans

\*Riluzole: PD, pharmacology

Signal Transduction: DE, drug effects

Signal Transduction: PH, physiology

\*Spinal Cord: DE, drug effects

Spinal Cord: ME, metabolism

Spinal Cord: UL, ultrastructure

\*Synaptosomes: DE, drug effects

Synaptosomes: ME, metabolism

Synaptosomes: UL, ultrastructure

RN 1744-22-5 (Riluzole); 56-86-0 (Glutamic Acid)

CN 0 (ATP-Binding Cassette Transporters); 0 (Amino Acid Transport System X-AG); EC 3.6.1.- (GTP-Binding Proteins)

L15 ANSWER 5 OF 18 MEDLINE

ACCESSION NUMBER: 2000469184 MEDLINE

DOCUMENT NUMBER: 20384315 PubMed ID: 10925226

TITLE: Ischemic spinal cord injury induced by aortic cross-clamping: prevention by riluzole.

AUTHOR: Lang-Lazdunski L; Heurteaux C; Mignon A; Mantz J; Widmann C; Desmonts J; Lazdunski M

CORPORATE SOURCE: Department of Cardiovascular Surgery, Hopital Bichat and Xavier Bichat Medical University, Paris, France..

loic.lang@wanadoo.fr

SOURCE: EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY, (2000 Aug) 18 (2) 174-81.

Journal code: 8804069. ISSN: 1010-7940.

PUB. COUNTRY: ENGLAND: United Kingdom

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200010

ENTRY DATE: Entered STN: 20001012

Last Updated on STN: 20001012

Entered Medline: 20001003

AB OBJECTIVE: Recent studies confirmed the deleterious role of glutamate in the pathophysiology of spinal cord ischemia induced by aortic cross-clamping. We investigated the effect of riluzole, an anti-glutamate drug, in a rat model of spinal cord ischemia. MATERIALS AND METHODS: Spinal cord ischemia was induced in normothermia for 14 min in Sprague-Dawley rats using direct aortic arch plus left subclavian artery cross-clamping through a limited thoracotomy. Experimental groups were as follows: sham-operation (n=15), control (n=15) receiving only vehicle,

riluzole (n=15) receiving riluzole (4 mg/kg) before clamping and at the onset of reperfusion. Separate animals were used for monitoring physiologic parameters in the sham-operation (n=3), control (n=5), and riluzole (n=5) groups. Neurologic status was assessed at 6, 24 h, and then daily up to 96 h. Rats were randomly killed at 24, 48, or 96 h (n=5 for each time). Spinal cords were harvested for histopathology, immunohistochemistry for microtubule-associated protein 2 (MAP-2), TUNEL staining, and analysis of DNA fragmentation by agarose gel electrophoresis. RESULTS: All sham-operated rats had a normal neurologic outcome, whereas all control rats suffered severe and definitive paraplegia. Riluzole-treated rats had significantly better neurologic function compared to the control. Histopathology disclosed severe neuronal necrosis in the lumbar gray matter of control rats, whereas riluzole-treated rats suffered usually mild to moderate injury. Riluzole particularly prevented motor neurons injury. MAP-2 immunoreactivity was completely lost in control rats, whereas it was preserved either completely or partly in riluzole-treated rats. TUNEL staining revealed numerous apoptotic neurons scattered within the whole gray matter of control rats. Riluzole prevented or dramatically attenuated apoptotic neuronal death in treated rats. DNA extracted from lumbar spinal cords of sham-operated and riluzole-treated rats exhibited no laddering, whereas spinal cords from control rats showed DNA laddering with fragmentation into approximately 180 multiples of base pairs. CONCLUSIONS: Riluzole may protect the spinal cord in a setting of severe ischemia by preventing neuronal necrosis and apoptosis. This drug may therefore be considered for clinical use during 'high risk' surgical procedures on the thoracoabdominal aorta.

CT Check Tags: Animal; Comparative Study; Male; Support, Non-U.S. Gov't  
 Aorta, Thoracic: SU, surgery  
 Apoptosis: DE, drug effects  
 Biological Markers  
 Electrophoresis, Agar Gel  
 \*Excitatory Amino Acid Antagonists: TU, therapeutic use  
 In Situ Nick-End Labeling  
 Ligation: AE, adverse effects  
 Microtubule-Associated Proteins: ME, metabolism  
 Necrosis  
 Neurons: ME, metabolism  
 Neurons: PA, pathology  
 Rats  
 Rats, Sprague-Dawley  
 \*Riluzole: TU, therapeutic use  
 Spinal Cord: ME, metabolism  
 \*Spinal Cord: PA, pathology  
 Spinal Cord Ischemia: ET, etiology  
 Spinal Cord Ischemia: ME, metabolism  
 Spinal Cord Ischemia: PA, pathology  
 \*Spinal Cord Ischemia: PC, prevention & control  
 RN 1744-22-5 (Riluzole)  
 CN 0 (Biological Markers); 0 (Excitatory Amino Acid Antagonists); 0  
 (Microtubule-Associated Proteins)

L15 ANSWER 6 OF 18 MEDLINE  
 ACCESSION NUMBER: 2000453566 MEDLINE  
 DOCUMENT NUMBER: 20464412 PubMed ID: 11011817  
 TITLE: Riluzole and methylprednisolone combined treatment improves functional recovery in traumatic spinal cord injury.

AUTHOR: Mu X; Azbill R D; Springer J E  
 CORPORATE SOURCE: Department of Anatomy and Neurobiology, University of  
 Kentucky Medical Center, Lexington 40536-0084, USA.  
 CONTRACT NUMBER: NS30248 (NINDS)  
 NS40015 (NINDS)  
 SOURCE: JOURNAL OF NEUROTRAUMA, (2000 Sep) 17 (9) 773-80.  
 Journal code: 8811626. ISSN: 0897-7151.  
 PUB. COUNTRY: United States  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 200102  
 ENTRY DATE: Entered STN: 20010322  
 Last Updated on STN: 20010322  
 Entered Medline: 20010201

AB The potential use of riluzole (a glutamate release inhibitor) alone or in combination with methyl-prednisolone (MP) in treating acute spinal cord injury (SCI) was examined. Rats received a contusion injury to the spinal cord using the NYU impactor and were treated with vehicle, riluzole (8 mg/kg), MP (30 mg/kg), or riluzole + MP at 2 and 4 h following injury. Animals continued to receive riluzole treatment (8 mg/kg) for a period of 1 week. The animals were then tested weekly for functional recovery using the BBB open field locomotor score. At the end of testing (6 weeks after injury), each spinal cord was examined for the amount of remaining tissue at the injury site and a myelination index was used to quantify remaining axons in the ventromedial white matter. In this study, only the combination treatment was found to significantly improve behavioral recovery as assessed using the BBB open field locomotor scale. In addition, the combination treatment promoted tissue sparing at the lesion epicenter, but had no clear effect on the index of myelination. The results of this study clearly demonstrate the potential beneficial effects of a combination approach in the treatment of traumatic SCI.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

Drug Therapy, Combination

\*Excitatory Amino Acid Antagonists: PD, pharmacology

Gait Disorders, Neurologic: DT, drug therapy

Gait Disorders, Neurologic: PA, pathology

Gait Disorders, Neurologic: RH, rehabilitation

\*Glucocorticoids, Synthetic: PD, pharmacology

Glutamic Acid: ME, metabolism

Locomotion: DE, drug effects

\*Methylprednisolone: PD, pharmacology

Myelin Sheath: PA, pathology

Myelin Sheath: PH, physiology

Rats

Rats, Long-Evans

Recovery of Function: DE, drug effects

\*Riluzole: PD, pharmacology

Spinal Cord: DE, drug effects

Spinal Cord: ME, metabolism

Spinal Cord: PA, pathology

\*Spinal Cord Injuries: DT, drug therapy

Spinal Cord Injuries: PA, pathology

Spinal Cord Injuries: RH, rehabilitation

RN 1744-22-5 (Riluzole); 56-86-0 (Glutamic Acid); 83-43-2  
 (Methylprednisolone)



CN 0 (Excitatory Amino Acid Antagonists); 0 (Glucocorticoids, Synthetic)

L15 ANSWER 7 OF 18 MEDLINE

ACCESSION NUMBER: 2000401930 MEDLINE

DOCUMENT NUMBER: 20329773 PubMed ID: 10869502

TITLE: Riluzole improves measures of oxidative stress following traumatic spinal cord injury.

AUTHOR: Mu X; Azbill R D; Springer J E

CORPORATE SOURCE: Department of Anatomy and Neurobiology, Center for Spinal Cord and Brain Injury Research, University of Kentucky Medical Center, 800 Rose Street, Lexington, KY 40536-0084, USA.

CONTRACT NUMBER: NS-30248 (NINDS)

NS40015 (NINDS)

SOURCE: BRAIN RESEARCH, (2000 Jul 7) 870 (1-2) 66-72.

Journal code: 0045503. ISSN: 0006-8993.

PUB. COUNTRY: Netherlands

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200008

ENTRY DATE: Entered STN: 20000901

Last Updated on STN: 20000901

Entered Medline: 20000821

AB Rats received a contusion injury to the spinal cord followed by treatment with riluzole (a glutamate release inhibitor, 8 mg/kg), methylprednisolone (MP 30 mg/kg) or both. At 4 h following injury, spinal cords were removed and synaptosomes prepared and examined using five measures of oxidative stress. Riluzole treatment was found to improve mitochondrial function, and enhance glutamate and glucose uptake. As expected, MP treatment was found to reduce lipid peroxidation, but also improved glutamate and glucose uptake. Interestingly, the combination treatment was found to be effective in improving all five measures of oxidative stress. The results of this study clearly demonstrate the potential beneficial effects of a combination approach in the treatment of oxidative stress events in traumatic spinal cord injury.

CT Check Tags: Animal; Female; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

Glutamic Acid: ME, metabolism

Glutamic Acid: TO, toxicity

Mitochondria: ME, metabolism

\*Neuroprotective Agents: PD, pharmacology

Neurotoxins: ME, metabolism

\*Oxidative Stress: DE, drug effects

Rats

Rats, Long-Evans

Rhodamines

\*Riluzole: PD, pharmacology

\*Spinal Cord Injuries: DT, drug therapy

\*Spinal Cord Injuries: ME, metabolism

Synaptosomes: ME, metabolism

Thiobarbituric Acid Reactive Substances: ME, metabolism

RN 109244-58-8 (dihydrorhodamine 123); 1744-22-5 (Riluzole); 56-86-0 (Glutamic Acid)

CN 0 (Neuroprotective Agents); 0 (Neurotoxins); 0 (Rhodamines); 0 (Thiobarbituric Acid Reactive Substances)

L15 ANSWER 8 OF 18 MEDLINE  
ACCESSION NUMBER: 2000336784 MEDLINE  
DOCUMENT NUMBER: 20336784 PubMed ID: 10876221  
TITLE: Prevention of ischemic spinal cord injury: comparative effects of magnesium sulfate and riluzole.  
AUTHOR: Lang-Lazdunski L; Heurteaux C; Dupont H; Widmann C; Lazdunski M  
CORPORATE SOURCE: Departments of Cardiovascular Surgery and Anesthesiology, Hopital Bichat and Xavier Bichat Medical University, Paris, France.  
SOURCE: JOURNAL OF VASCULAR SURGERY, (2000 Jul) 32 (1) 179-89. Journal code: 8407742. ISSN: 0741-5214.  
PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)  
LANGUAGE: English  
FILE SEGMENT: Priority Journals  
ENTRY MONTH: 200008  
ENTRY DATE: Entered STN: 20000811  
Last Updated on STN: 20000811  
Entered Medline: 20000802

AB PURPOSE: Excitotoxic mechanisms have been implicated in the pathophysiology of spinal cord ischemic injury induced by aortic cross-clamping. We investigated the effects of the anti-excitotoxic drugs magnesium sulfate (MgSO(4)) and riluzole in a rabbit model of spinal cord ischemia. METHOD: The infrarenal aorta of New Zealand albino white rabbits (n = 68) was occluded for 40 minutes. Experimental groups included: a control group, which received only vehicle (n = 17); group A (n = 17), which received riluzole (8 mg/kg) before clamping; group B (n = 17), which received MgSO(4) (100 mg/kg) before clamping; and group C (n = 17), which received riluzole (8 mg/kg) and MgSO(4) (100 mg/kg) before clamping. Five additional rabbits had the same operation, but did not undergo aortic clamping (sham operation). The neurological status of the rabbits was assessed at 24 hours, 48 hours, and then daily for as long as 120 hours by using a modified Tarlov scale. The rabbits were killed at 24 hours (n = 3 per group), 48 hours (n = 4 per group), and 120 hours (n = 10 per group) postoperatively. Spinal cords were harvested for histopathologic and immunohistochemistry examinations for microtubule-associated protein-2 (MAP-2), a cytoskeletal protein specific from neurons. RESULTS: No major adverse effect was observed with either riluzole or MgSO(4). All control rabbits became severely paraplegic. All riluzole-treated and MgSO(4)-treated animals had a better neurological status than control animals. Typical morphological changes characteristic of neuronal necrosis in the gray matter of control animals was demonstrated by means of the histopathological examination, whereas riluzole or magnesium prevented or attenuated necrotic phenomena. Moreover, MAP-2 immunoreactivity was completely lost in control rabbits, whereas it was preserved, either completely or partially, in rabbits treated with riluzole or magnesium. Riluzole was more effective than MgSO(4) in preventing paraplegia caused by motor neuron injury (P < .01). Riluzole and MgSO(4) had no additive neuroprotective effect. CONCLUSION: These results demonstrate that riluzole and, to a lesser extent, MgSO(4) may afford significant spinal cord protection in a setting of severe ischemia and may, therefore, be considered for clinical use during "high-risk" operations on the thoracic and thoracoabdominal aorta.

CT Check Tags: Animal; Comparative Study; Female; Support, Non-U.S. Gov't  
Aorta  
Aorta, Thoracic: SU, surgery

Constriction  
 Immunohistochemistry  
 \*Ischemia: PC, prevention & control  
 \*Magnesium Sulfate: TU, therapeutic use  
 Microtubule-Associated Proteins: ME, metabolism  
 \*Neuroprotective Agents: TU, therapeutic use  
 Paraplegia: PC, prevention & control  
 Rabbits  
 \*Receptors, N-Methyl-D-Aspartate: AI, antagonists & inhibitors  
   **\*Riluzole: TU, therapeutic use**  
   **\*Spinal Cord: BS, blood supply**  
 Treatment Outcome  
 RN 1744-22-5 (Riluzole); 7487-88-9 (Magnesium Sulfate)  
 CN 0 (Microtubule-Associated Proteins); 0 (Neuroprotective Agents); 0  
 (Receptors, N-Methyl-D-Aspartate)

L15 ANSWER 9 OF 18 MEDLINE  
 ACCESSION NUMBER: 2000063827 MEDLINE  
 DOCUMENT NUMBER: 20063827 PubMed ID: 10596003  
 TITLE: A word of caution in extrapolating the riluzole spinal cord  
 injury protective effects obtained in a rabbit model under  
 ketamine anesthesia.  
 COMMENT: Comment on: J Thorac Cardiovasc Surg. 1999 May;117(5):881-9  
 AUTHOR: Miyamoto T A; Miyamoto K J  
 SOURCE: JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, (1999 Dec)  
 118 (6) 1156-7.  
 Journal code: 0376343. ISSN: 0022-5223.  
 PUB. COUNTRY: United States  
 Commentary  
 Letter  
 LANGUAGE: English  
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals  
 ENTRY MONTH: 199912  
 ENTRY DATE: Entered STN: 20000113  
 Last Updated on STN: 20000314  
 Entered Medline: 19991223

CT Check Tags: Animal  
 \*Anesthetics, Dissociative: AD, administration & dosage  
 Cardiopulmonary Bypass: AE, adverse effects  
 Disease Models, Animal  
 Drug Synergism  
 Excitatory Amino Acid Antagonists: AD, administration & dosage  
 \*Excitatory Amino Acid Antagonists: TU, therapeutic use  
 Follow-Up Studies  
 \*Ischemia: PC, prevention & control  
 \*Ketamine: AD, administration & dosage  
 Neurologic Examination  
 \*Neuroprotective Agents: TU, therapeutic use  
 Rabbits  
   **\*Riluzole: TU, therapeutic use**  
   **\*Spinal Cord: BS, blood supply**  
   **Spinal Cord: DE, drug effects**  
 RN 1744-22-5 (Riluzole); 6740-88-1 (Ketamine)  
 CN 0 (Anesthetics, Dissociative); 0 (Excitatory Amino Acid Antagonists); 0  
 (Neuroprotective Agents)

L15 ANSWER 10 OF 18 MEDLINE

ACCESSION NUMBER: 2000009716 MEDLINE  
 DOCUMENT NUMBER: 20009716 PubMed ID: 10540024  
 TITLE: Prevention by insulin-like growth factor-I and riluzole in motor neuron death after neonatal axotomy.  
 AUTHOR: Iwasaki Y; Ikeda K  
 CORPORATE SOURCE: The Fourth Department of Internal Medicine, Toho University Ohashi Hospital, 2-17-6, Ohashi, Meguro-ku, Tokyo, Japan.  
 SOURCE: JOURNAL OF THE NEUROLOGICAL SCIENCES, (1999 Oct 31) 169 (1-2) 148-55.  
 Journal code: 0375403. ISSN: 0022-510X.  
 PUB. COUNTRY: Netherlands  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199912  
 ENTRY DATE: Entered STN: 20000113  
 Last Updated on STN: 20000113  
 Entered Medline: 19991202

AB Transection of the sciatic nerve in neonatal rats results discernable loss of motor neurons in the spinal cord. This neuronal death could be due to lack of retrogradely transported target derived neurotrophic factors, since some of these factors have been shown to be effective in injury induced motor neuron death. Another hypothesis suggests that glutamate and its receptors has been implicated as possible mechanism for motor neuron death, because inhibitor of glutamate release and antagonists of glutamate receptors are effective in preventing axotomized motor neuron death. To investigate the effect of insulin-like growth factor-I (IGF-I) and riluzole, a drug that inhibits glutamate release, on axotomy induced motor neuron death. Newborn rats were anesthetized with hypothermia. Sciatic nerve was cut near the obturator tendon in the left thigh. Animals were then treated daily with different doses of IGF-I and riluzole for 14 days with intraperitoneal injections. Control rats received PBS in the same fashion. After the treatment, the number of surviving motor neurons and the motor neuron diameter in the L(4) was assessed. Both IGF-I (1.0 mg/kg) and riluzole (5.0 mg/kg) rescued motor neuron death in a similar way. Co-administration of IGF-I (1.0 mg/kg) and riluzole (5.0 mg/kg) was more effective than either agent alone and there was a statistically significant difference between co-administration and IGF-I alone. However there was no significant difference between simultaneous treatment and riluzole alone. As for diameter of motor neurons, riluzole (5.0 mg/kg) preserved the motor neuron diameter in the lesion side. Nonetheless, no further increase in motor neuron diameter was seen when riluzole (5 mg/kg) and IGF-I (1.0 mg/kg) were applied in combination. Both agents did not affect diameter of motor neurons in the non-axotomy side. Riluzole is available in amyotrophic lateral sclerosis (ALS) and the positive results of clinical trials with IGF-I suggests that combination treatment of IGF-I and riluzole in ALS remains to be determined.

CT Check Tags: Animal  
 Animals, Newborn  
 Axotomy  
 Cell Death: DE, drug effects  
 Cell Death: PH, physiology  
 \*Insulin-Like Growth Factor I: PD, pharmacology  
 \*Motor Neurons: DE, drug effects  
 Motor Neurons: PH, physiology  
 \*Neuroprotective Agents: PD, pharmacology  
 Rats

Rats, Sprague-Dawley

\*Riluzole: PD, pharmacology

Sciatic Nerve: DE, drug effects

Sciatic Nerve: PH, physiology

\*Spinal Cord: DE, drug effects

Spinal Cord: PH, physiology

RN 1744-22-5 (Riluzole); 67763-96-6 (Insulin-Like Growth Factor I)

CN 0 (Neuroprotective Agents)

L15 ANSWER 11 OF 18 MEDLINE

ACCESSION NUMBER: 1999424138 MEDLINE

DOCUMENT NUMBER: 99424138 PubMed ID: 10494351

TITLE: Neuroprotective effects of riluzole in neurotrauma models: a review.

AUTHOR: Wahl F; Stutzmann J M

CORPORATE SOURCE: Neurodegenerative Diseases Department, Rhone-Poulenc Rorer, CRVA, France.

SOURCE: ACTA NEUROCHIRURGICA. SUPPLEMENTUM, (1999) 73 103-10. Journal code: 0140560. ISSN: 0065-1419.

PUB. COUNTRY: Austria

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199910

ENTRY DATE: Entered STN: 19991101

Last Updated on STN: 19991101

Entered Medline: 19991020

AB Physical injury to the central nervous system (CNS) remains one of the main causes of mortality and disability in young adults. Numerous therapies have been successfully evaluated in experimental traumatic brain or spinal cord injuries (TBI, SCI) and, although some of them are currently under clinical trials for these indications, no drug therapy is at present available. Thus, an interesting approach to reduce the CNS injury-induced damage could be the blockade of Na(+)-channels by drugs such as riluzole which is neuroprotective in models of TBI or SCI as summarized in this review. Repeated doses ranging from 2 to 8 mg/kg were administered between 24 h to 10 days post-injury, with a first administration given either at 15 min or up to 6 h post-injury. In these models riluzole was found to reduce both the size of spinal cord and brain lesions as well as brain edema, and to restore the neurological, motor and cognitive impairments consequent of these injuries. The largest therapeutic time window obtained was 1 to 6 h in TBI. This such a compound should be considered as an interesting candidate for the treatment or SCI or TBI.

CT Check Tags: Animal

Brain Edema: DT, drug therapy

Brain Injuries: DI, diagnosis

\*Brain Injuries: DT, drug therapy

Brain Injuries: PA, pathology

Brain Injuries: PP, physiopathology

Brain Injuries: PX, psychology

Cognition

Evoked Potentials, Somatosensory: DE, drug effects

Memory: DE, drug effects

Neurologic Examination

\*Neuroprotective Agents: TU, therapeutic use

Rats

Rats, Sprague-Dawley

Rats, Wistar

\*Riluzole: TU, therapeutic use

\*Spinal Cord Injuries: DT, drug therapy

Spinal Cord Injuries: PA, pathology

Spinal Cord Injuries: PP, physiopathology

Wounds, Nonpenetrating: DI, diagnosis

Wounds, Nonpenetrating: DT, drug therapy

Wounds, Nonpenetrating: PA, pathology

Wounds, Nonpenetrating: PP, physiopathology

Wounds, Nonpenetrating: PX, psychology

RN 1744-22-5 (Riluzole)

CN 0 (Neuroprotective Agents)

L15 ANSWER 12 OF 18 MEDLINE

ACCESSION NUMBER: 199238751 MEDLINE

DOCUMENT NUMBER: 99238751 PubMed ID: 10220679

TITLE: Riluzole prevents ischemic spinal cord injury caused by aortic crossclamping.

COMMENT: Comment in: J Thorac Cardiovasc Surg. 1999 Dec;118(6):1156-7

AUTHOR: Lang-Lazdunski L; Heurteaux C; Vaillant N; Widmann C; Lazdunski M

CORPORATE SOURCE: Department of Cardiovascular Surgery, Paris, and the Institute of Molecular and Cellular Pharmacology, Valbonne, France.

SOURCE: JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY, (1999 May) 117 (5) 881-9.

Journal code: 0376343. ISSN: 0022-5223.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals

ENTRY MONTH: 199905

ENTRY DATE: Entered STN: 19990601

Last Updated on STN: 20000314

Entered Medline: 19990518

AB BACKGROUND: Recent studies support the involvement of glutamate neurotoxicity in the pathophysiology of spinal cord injury induced by aortic crossclamping. We investigated the effects of riluzole, a neuroprotective drug that blocks glutamatergic neurotransmission, in a rabbit model of spinal cord ischemia. METHODS: The infrarenal aortas of New Zealand White albino rabbits (n = 40) were occluded for 40 minutes. Experimental groups were as follows: sham operation group (n = 5), control group undergoing occlusion but receiving no pharmacologic intervention (n = 10), experimental group A (n = 10) receiving 8 mg/kg riluzole intravenously 30 minutes before ischemia, experimental group B (n = 10) receiving 4 mg/kg riluzole intravenously 30 minutes before ischemia and at the onset of reperfusion, and experimental group C (n = 10) receiving 8 mg/kg riluzole intravenously at the onset of reperfusion. Neurologic status was assessed at 6, 24, and 48 hours after the operation and then daily until the fifth day. All animals were killed at 24, 48, or 120 hours after the operation. Spinal cords were harvested for histopathologic studies, immunohistochemical studies for microtubule-associated protein 2, and search for morphologic features of apoptosis by the terminal deoxynucleotidyltransferase-mediated deoxyuridine triphosphate-biotin nick-end labeling staining method. RESULTS: All animals in the control

group became paraplegic. Except for 1 rabbit in group C, all riluzole-treated animals had better neurologic function. Luxol fast blue and terminal deoxynucleotidyltransferase-mediated deoxyuridine triphosphate-biotin nick-end labeling staining methods demonstrated typical morphologic changes characteristic of necrosis and apoptosis in control animals. Riluzole prevented or attenuated ischemia-induced necrosis, apoptosis, and cytoskeletal proteolysis, depending on the dose and the timing of administration. CONCLUSION: Riluzole may have therapeutic utility during high-risk operations on the thoracoabdominal aorta.

CT Check Tags: Animal; Comparative Study; Female; Support, Non-U.S. Gov't  
 Aorta, Abdominal: SU, surgery  
 Apoptosis: GE, genetics  
 Constriction  
 Cytoplasm: ME, metabolism  
 DNA: AN, analysis  
 DNA Fragmentation  
 Disease Models, Animal  
 Immunoenzyme Techniques  
 In Situ Nick-End Labeling  
 Injections, Intravenous  
 Ischemia: ME, metabolism  
 Ischemia: PA, pathology  
 \*Ischemia: PC, prevention & control  
 Microtubule-Associated Proteins: ME, metabolism  
 Motor Neurons: DE, drug effects  
 Motor Neurons: ME, metabolism  
 Motor Neurons: PA, pathology  
 Necrosis  
 Neuroprotective Agents: AD, administration & dosage  
 \*Neuroprotective Agents: TU, therapeutic use  
 Photomicrography  
 Rabbits  
     Riluzole: AD, administration & dosage  
     \*Riluzole: TU, therapeutic use  
     \*Spinal Cord: BS, blood supply  
     Spinal Cord: DE, drug effects  
     Spinal Cord: ME, metabolism  
 RN 1744-22-5 (Riluzole); 9007-49-2 (DNA)  
 CN 0 (Microtubule-Associated Proteins); 0 (Neuroprotective Agents)

L15 ANSWER 13 OF 18 MEDLINE  
 ACCESSION NUMBER: 1998163997 MEDLINE  
 DOCUMENT NUMBER: 98163997 PubMed ID: 9503266  
 TITLE: The glutamate antagonist riluzole suppresses intracortical facilitation.  
 AUTHOR: Liepert J; Schwenkreis P; Tegenthoff M; Malin J P  
 CORPORATE SOURCE: Department of Neurology, Ruhr University Bochum, Federal Republic of Germany.  
 SOURCE: JOURNAL OF NEURAL TRANSMISSION, (1997) 104 (11-12) 1207-14.  
 Journal code: 9702341. ISSN: 0300-9564.  
 PUB. COUNTRY: Austria  
                   (CLINICAL TRIAL)  
                   Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199804

ENTRY DATE: Entered STN: 19980507

Last Updated on STN: 19980507

Entered Medline: 19980429

AB The effect of the glutamate antagonist riluzole on excitatory and inhibitory phenomena in the human motor system was studied by transcranial magnetic stimulation (TMS) and peripheral electrical nerve stimulation. The motor threshold, the intracortical inhibition and intracortical facilitation as assessed by paired TMS, the cortical and peripheral silent periods, F wave amplitudes and F wave latencies were measured. Riluzole suppressed the intracortical facilitation whereas other parameters remained unchanged, indicating that the neurotransmitter glutamate is mainly involved in facilitatory mechanisms in the motor system.

CT Check Tags: Human

Adult

Cerebral Cortex: DE, drug effects

\*Cerebral Cortex: PH, physiology

Electromagnetic Fields

Electrophysiology

Excitatory Amino Acid Antagonists: AE, adverse effects

\*Excitatory Amino Acid Antagonists: PD, pharmacology

\*Glutamic Acid: PH, physiology

Movement: DE, drug effects

Movement: PH, physiology

Peripheral Nervous System: DE, drug effects

Peripheral Nervous System: PH, physiology

Riluzole: AE, adverse effects

\*Riluzole: PD, pharmacology

Spinal Cord: DE, drug effects

RN 1744-22-5 (Riluzole); 56-86-0 (Glutamic Acid)

CN 0 (Excitatory Amino Acid Antagonists)

L15 ANSWER 14 OF 18

MEDLINE

ACCESSION NUMBER: 97465568 MEDLINE

DOCUMENT NUMBER: 97465568 PubMed ID: 9326288

TITLE: Rapid calpain I activation and cytoskeletal protein degradation following traumatic spinal cord injury: attenuation with riluzole pretreatment.

AUTHOR: Springer J E; Azbill R D; Kennedy S E; George J; Geddes J W

CORPORATE SOURCE: Department of Anatomy and Neurobiology, University of Kentucky Medical Center, Lexington 40536-0084, U.S.A.

CONTRACT NUMBER: AG-08974 (NIA)  
NS-30248 (NINDS)SOURCE: JOURNAL OF NEUROCHEMISTRY, (1997 Oct) 69 (4) 1592-600.  
Journal code: 2985190R. ISSN: 0022-3042.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199710

ENTRY DATE: Entered STN: 19971224

Last Updated on STN: 19971224

Entered Medline: 19971027

AB Immunocytochemical and immunoblotting techniques were used to investigate calpain I activation and the stability of the calpain-sensitive cytoskeletal proteins microtubule-associated protein 2 (MAP2) and spectrin at 1, 4, and 24 h after contusion injury to the spinal cord. Spinal cord injury resulted in the activation of calpain I at all time points



examined, with the highest level of activation occurring at 1 h. At the same early time point, there was a loss of dendritic MAP2 staining in spinal cord sections, accompanied by pronounced perikaryal accumulation. The loss in MAP2 staining in the injured spinal cord progressed over the 24-h survival period to affect regions 3 mm distant to the site of injury. The presence of calpain I-specific spectrin degradation was apparent in neuronal cell bodies and fibers as early as 1 h after injury, with the most intense staining occurring within and juxtaposed to the injury site. Spectrin breakdown products in neuronal cell bodies declined rapidly at 4 h and were nearly undetectable at 24 h after injury. Immunoblot studies confirmed the immunocytochemical results by demonstrating a significant increase in calpain I activation, a significant decrease in MAP2 levels, and a significant increase in spectrin breakdown. Finally, treatment of animals with riluzole, an inhibitor of glutamate release, before surgery reduced significantly the loss of MAP2 levels observed at 24 h after injury. These results demonstrate that Ca<sup>2+</sup>-dependent protease activation and degradation of critical cytoskeletal proteins are early events after spinal cord injury and that treatments that minimize the actions of glutamate may limit their breakdown.

CT Check Tags: Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

\*Calpain: ME, metabolism

\*Contusions: ME, metabolism

\*Cytoskeletal Proteins: ME, metabolism  
Enzyme Activation

\*Excitatory Amino Acid Antagonists: PD, pharmacology  
Immunohistochemistry

Microtubule-Associated Proteins: ME, metabolism  
Rats

\*Riluzole: PD, pharmacology

Spectrin: ME, metabolism

\*Spinal Cord Injuries: ME, metabolism

RN 12634-43-4 (Spectrin); 1744-22-5 (Riluzole)

CN 0 (Cytoskeletal Proteins); 0 (Excitatory Amino Acid Antagonists); 0  
(Microtubule-Associated Proteins); EC 3.4.22.17 (Calpain)

L15 ANSWER 15 OF 18 MEDLINE

ACCESSION NUMBER: 97361683 MEDLINE

DOCUMENT NUMBER: 97361683 PubMed ID: 9218644

TITLE: Riluzole promotes survival of rat motoneurons in vitro by stimulating trophic activity produced by spinal astrocyte monolayers.

AUTHOR: Peluffo H; Estevez A; Barbeito L; Stutzmann J M

CORPORATE SOURCE: Instituto Clemente Estable and Facultad de Ciencias, Montevideo, Uruguay.

SOURCE: NEUROSCIENCE LETTERS, (1997 Jun 13) 228 (3) 207-11.  
Journal code: 7600130. ISSN: 0304-3940.

PUB. COUNTRY: Ireland  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199709

ENTRY DATE: Entered STN: 19970916

Last Updated on STN: 19980206

Entered Medline: 19970902

AB In the present study we have assessed whether riluzole stimulates the production of trophic activities for motoneurons by spinal astrocyte cultures. Astrocyte monolayers prepared from new-born rats were exposed to

vehicle or riluzole (1-10 microM) for 30-36 h, then washed and further incubated without riluzole for 24 h in L15 medium to obtain the astrocyte conditioned media (ACM). Motoneuron-enriched cultures were used to test the ability of the ACM to support motoneuron viability. Astrocyte monolayers exposed to 1 microM riluzole did not show changes in morphology or in DNA or protein synthesis. However, the conditioned medium obtained from astrocyte monolayers after this treatment increased motoneuron survival compared to that from vehicle-treated cultures. A similar effect was found when astrocytes were exposed to a higher riluzole concentration (10 microM) but with greater dilutions of the conditioned medium. This trophic activity was abolished by boiling or after treatment with trypsin. These findings strongly suggest the existence of a new trophic mechanism, through which riluzole may exert motoneuron protection.

CT Check Tags: Animal

\*Astrocytes: DE, drug effects

Cell Survival: DE, drug effects

Cells, Cultured

Culture Media, Conditioned

DNA: BI, biosynthesis

Immunohistochemistry

Leucine: ME, metabolism

\*Motor Neurons: DE, drug effects

Nerve Tissue Proteins: BI, biosynthesis

\*Neuroprotective Agents: PD, pharmacology

Rats

Receptors, Nerve Growth Factor: BI, biosynthesis

Riluzole

\*Spinal Cord: CY, cytology

Spinal Cord: DE, drug effects

\*Thiazoles: PD, pharmacology

Thymidine: ME, metabolism

RN 1744-22-5 (Riluzole); 50-89-5 (Thymidine); 61-90-5 (Leucine); 9007-49-2 (DNA)

CN 0 (Culture Media, Conditioned); 0 (Nerve Tissue Proteins); 0 (Neuroprotective Agents); 0 (Receptors, Nerve Growth Factor); 0 (Thiazoles)

L15 ANSWER 16 OF 18 MEDLINE

ACCESSION NUMBER: 96290627 MEDLINE

DOCUMENT NUMBER: 96290627 PubMed ID: 8730788

TITLE: The effect of riluzole on post-traumatic spinal cord injury in the rat.

AUTHOR: Stutzmann J M; Pratt J; Boraud T; Gross C

CORPORATE SOURCE: Neurodegenerative Diseases Department, Rhine-Poulenc Rorer, CRVA, Vitry, France.

SOURCE: NEUROREPORT, (1996 Jan 31) 7 (2) 387-92.  
Journal code: 9100935. ISSN: 0959-4965.

PUB. COUNTRY: ENGLAND: United Kingdom  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199611

ENTRY DATE: Entered STN: 19961219

Last Updated on STN: 19980206

Entered Medline: 19961125

AB This study evaluated treatment with riluzole, a neuroprotective agent, following thoracic spinal cord compression in the rat. Animals received

riluzole (2 mg kg<sup>-1</sup>) or vehicle twice daily for 10 days following the trauma. Motor deficits, somatosensory evoked potentials (SEP) and lesion histology were evaluated. Although paralysis was seen following trauma, seven of 10 animals receiving riluzole recovered motor function and nearly normal behaviour, unlike animals receiving vehicle. Trauma dramatically disturbed SEPs with falls in amplitude and increases in latency. After riluzole SEP returned towards pre-injury levels, while untreated animals showed no recovery. Morphological studies revealed significant (53%) reduction in the degree of spinal cord infarcted after riluzole treatment.

CT Check Tags: Animal; Male

Anesthesia

Evoked Potentials, Somatosensory: DE, drug effects

Hemorrhage: PP, physiopathology

\*Neuroprotective Agents: TU, therapeutic use

Paralysis: DT, drug therapy

Paralysis: PP, physiopathology

Rats

Rats, Wistar

Riluzole

Spinal Cord: PA, pathology

\*Spinal Cord Compression: DT, drug therapy

Spinal Cord Compression: PA, pathology

Spinal Cord Compression: PP, physiopathology

\*Thiazoles: TU, therapeutic use

Time Factors

RN 1744-22-5 (Riluzole)

CN 0 (Neuroprotective Agents); 0 (Thiazoles)

L15 ANSWER 17 OF 18 MEDLINE

ACCESSION NUMBER: 96197937 MEDLINE

DOCUMENT NUMBER: 96197937 PubMed ID: 8967745

TITLE: Benefit of vitamin E, riluzole, and gabapentin in a transgenic model of familial amyotrophic lateral sclerosis.

COMMENT: Comment in: Ann Neurol. 1996 Feb;39(2):145-6

AUTHOR: Gurney M E; Cutting F B; Zhai P; Doble A; Taylor C P; Andrus P K; Hall E D

CORPORATE SOURCE: Department of Cell and Molecular Biology, Northwestern University Medical School, Chicago, IL, USA.

SOURCE: ANNALS OF NEUROLOGY, (1996 Feb) 39 (2) 147-57.  
Journal code: 7707449. ISSN: 0364-5134.

PUB. COUNTRY: United States  
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199612

ENTRY DATE: Entered STN: 19970128

Last Updated on STN: 19980206

Entered Medline: 19961212

AB Familial amyotrophic lateral sclerosis (FALS) has been linked in some families to dominant mutations of the SOD1 gene encoding Cu,Zn superoxide dismutase (Cu,ZnSOD). We have used a transgenic model of FALS based on expression of mutant human Cu,ZnSOD to explore the etiology and therapy of the genetic disease. Expression of mutant, but not wild-type, human Cu,ZnSOD in mice places the brain and spinal cord under oxidative stress. This causes depletion of vitamin E, rather than the typical age-dependent increase in vitamin E content as occurs in nontransgenic mice and in mice expressing wild-type human Cu,ZnSOD. Dietary supplementation with vitamin

E delays onset of clinical disease and slows progression in the transgenic model but does not prolong survival. In contrast, two putative inhibitors of the glutamatergic system, riluzole and gabapentin, prolong survival. However, riluzole did not delay disease onset. Thus, there was clear separation of effects on onset, progression, and survival by the three therapeutics tested. This suggests the hypothesis that oxidative damage produced by the expression of mutant Cu,ZnSOD causes slow or weak excitotoxicity that can be inhibited in part by alerting glutamate release or biosynthesis presynaptically.

CT Check Tags: Animal; Human  
 \*Acetic Acids: TU, therapeutic use  
 Amyotrophic Lateral Sclerosis: DT, drug therapy  
 \*Amyotrophic Lateral Sclerosis: GE, genetics  
 Amyotrophic Lateral Sclerosis: ME, metabolism  
 Brain: ME, metabolism  
 Diet  
 Disease Progression  
 Mice  
 Mice, Transgenic  
 Oxidative Stress  
 Riluzole  
 Spinal Cord: ME, metabolism  
 Superoxide Dismutase: GE, genetics  
 Survival Analysis  
 \*Thiazoles: TU, therapeutic use  
 Vitamin E: AD, administration & dosage  
 \*Vitamin E: TU, therapeutic use  
 RN 1406-18-4 (Vitamin E); 1744-22-5 (Riluzole); 60142-96-3 (gabapentin)  
 CN 0 (Acetic Acids); 0 (Thiazoles); EC 1.15.1.1 (Superoxide Dismutase)

L15 ANSWER 18 OF 18 MEDLINE  
 ACCESSION NUMBER: 90374172 MEDLINE  
 DOCUMENT NUMBER: 90374172 PubMed ID: 1975768  
 TITLE: In vivo evidence for an inhibitory glutamatergic control of serotonin release in the cat caudate nucleus: involvement of GABA neurons.  
 AUTHOR: Becquet D; Faudon M; Héry F  
 CORPORATE SOURCE: Laboratoire de Neuroendocrinologie Experimentale, Faculte de Medecine Nord, I.N.S.E.R.M. U.297, Marseille, France.  
 SOURCE: BRAIN RESEARCH, (1990 Jun 11) 519 (1-2) 82-8.  
 Journal code: 0045503. ISSN: 0006-8993.  
 PUB. COUNTRY: Netherlands  
 Journal; Article; (JOURNAL ARTICLE)  
 LANGUAGE: English  
 FILE SEGMENT: Priority Journals  
 ENTRY MONTH: 199010  
 ENTRY DATE: Entered STN: 19901122  
 Last Updated on STN: 19980206  
 Entered Medline: 19901016  
 AB The local effect of L-glutamic acid ( $5 \times 10^{-5}$  M) on the release of [3H]serotonin continuously synthesized from [3H]tryptophan was examined in the caudate nucleus of 'encephale isole' unanaesthetized cats implanted with push-pull cannula. L-Glutamic acid ( $5 \times 10^{-5}$  M) decreased [3H]serotonin release from nerve terminals of the dorsalis raphe-striatal serotonergic neurons. The effect was antagonized by 2-amino-6-trifluoromethoxybenzothiazole (PK 26124) ( $10^{-6}$  M), an antagonist of glutamatergic transmission. This effect was mimicked by

N-methoxy-D-aspartic acid NMDA ( $5 \times 10^{-5}$  M) and prevented by DL-2-phosphono-valeric acid (APV) ( $5 \times 10^{-6}$  M), indicating that L-glutamic acid decreased serotonin release via a N-methoxy-D-aspartate type receptor. The superfusion of serotonergic nerve terminals in the caudate nucleus with tetrodotoxin prevented the inhibitory L-glutamic acid-induced effect on serotonin release. Furthermore, L-glutamic acid-induced inhibition of [3H]serotonin release was antagonized by bicuculline ( $5 \times 10^{-5}$  M). These data suggest that the glutamatergic receptors involved were not located directly on serotonin nerve terminals. The inhibitory control exerted by L-glutamic acid on serotonergic transmission could involve gamma-aminobutyric acid interneurons. Since no reduction of spontaneous [3H]serotonin release was observed in the presence of bicuculline, GABAergic neurons appeared to exert a phasic influence on serotonin release. Indirect inhibitory presynaptic control on serotonin release mediated by corticostriatal glutamatergic fibers is discussed in light of previous findings.

- CT Check Tags: Animal; Female; Male  
 2-Amino-5-phosphonovalerate: PD, pharmacology  
 Aspartic Acid: AA, analogs & derivatives  
 Aspartic Acid: PD, pharmacology  
 Bicuculline: PD, pharmacology  
 Cats  
 Caudate Nucleus: DE, drug effects  
 \*Caudate Nucleus: PH, physiology  
 Glutamates: PD, pharmacology  
 \*Glutamates: PH, physiology  
 Glutamic Acid  
 N-Methylaspartate  
 Neurons: DE, drug effects  
 \*Neurons: PH, physiology  
**Riluzole**  
 \*Serotonin: SE, secretion  
**Spinal Cord: PH, physiology**  
 Synaptic Transmission: DE, drug effects  
 Tetrodotoxin: PD, pharmacology  
 Thiazoles: PD, pharmacology  
 \*gamma-Aminobutyric Acid: PH, physiology
- RN 1744-22-5 (Riluzole); 4368-28-9 (Tetrodotoxin); 485-49-4 (Bicuculline);  
 50-67-9 (Serotonin); 56-12-2 (gamma-Aminobutyric Acid); 56-84-8 (Aspartic  
 Acid); 56-86-0 (Glutamic Acid); 6384-92-5 (N-Methylaspartate); 76726-92-6  
 (2-Amino-5-phosphonovalerate)
- CN 0 (Glutamates); 0 (Thiazoles)